Performance of the SCORTEN During the First Five Days of Hospitalization to Predict the Prognosis of Epidermal Necrolysis

Sarah Guégan[1], Sylvie Bastuji-Garin[2], Ewa Poszepczynska-Guigné[1], Jean-Claude Roujeau[1] and Jean Revuz[1]

The SCORTEN, calculated within 24 hours of admission, is a severity-of-illness score validated for toxic epidermal necrolysis and Stevens–Johnson syndrome. Our purpose was to assess the performance of successive SCORTEN during the first 5 days of hospitalization and to determine the influence of admission delay. Charts of 144 patients aged 46.8 years (±19.7), admitted to our department (1993–2003) with Stevens–Johnson syndrome or toxic epidermal necrolysis, were reviewed. Successive SCORTEN were compared between deceased patients ($n=28$, 19.4%) and survivors ($n=116$). The performance of the score (calibration, discrimination) was assessed on days 1–5. All seven SCORTEN variables, on days 1–5, were associated with a higher mortality rate. The SCORTEN rose slightly during hospitalization, with a significant difference between days 1 and 4 (<0.05). Performance of the SCORTEN was good on each day, but slightly better on day 3. The areas under the receiver-operating characteristic curves were above 80%. The admission delay did not differ between deceased patients and survivors. Delay-adjusted SCORTEN was close to the crude SCORTEN. The SCORTEN performance during the first 5 days of hospitalization was excellent, and at its best on day 3. We recommend to compute again the SCORTEN on day 3. The admission delay did not influence prognosis or SCORTEN.

Journal of Investigative Dermatology (2006) **126,** 272–276. doi:10.1038/sj.jid.5700068; published online 22 December 2005

INTRODUCTION

Toxic epidermal necrolysis (TEN) and Stevens–Johnson syndrome (SJS) are rare – 1.5–2 new cases per million population per year – drug-related, acute skin reactions (Roujeau and Stern, 1994). The overall mortality is 20–30%.

SJS and TEN are closely related diseases, characterized by sudden apoptosis of keratinocytes leading to mucous membrane erosions and epidermal detachment. Within this spectrum of epidermal necrolysis, detachment of less than 10% of the total body surface area defines SJS; when superior to 30%, it defines TEN, while intermediate cases are called SJS/TEN overlap (Bastuji-Garin *et al.*, 1993).

The SCORTEN is a SJS/TEN-specific severity-of-illness score based on a minimal set of well-defined variables (Bastuji-Garin *et al.*, 2000), evaluated during the 24 hours after patient admission to hospital. As shown in Table 1, seven predictive factors were identified and allotted equal weighting in the score, so that the SCORTEN ranged from 0 (no factor present) to 7 (all factors present). The score was validated and is currently used by several teams (Campione *et al.*, 2003; Trent *et al.*, 2003; Brown *et al.*, 2004; Trent *et al.*, 2004).

The clinicians' experience suggests that, in a majority of patients, the disease progresses during a few days following admission, which could result in an increase in the SCORTEN. The purpose of this study was to assess the predictive value of the same score when performed later during hospitalization. We also analyzed the influence of admission delay on the mortality.

RESULTS

Study population

The database included 144 patients, 74 were males (51.4%), the mean age was 46.8 (19.7). The median (interquartile range) admission delay was 4.5 days (3–7). In total, 72% of these patients (ie 104) had been included in the two databases used for the initial SCORTEN development and assessment. In all, 28 patients died, the mortality rate at discharge from hospital was 19.4% (95% confidence interval 13.0–25.9).

Mortality according to the day 1 SCORTEN

Figure 1 shows the cumulative proportions of survivors according to the day 1 SCORTEN level; logrank analysis evidenced a highly significant difference between survival curves ($P<0.0001$). The estimated probability of 60-day

[1]*Department of Dermatology, Henri-Mondor Hospital (AP-HP), University Paris XII, Créteil, France and* [2]*Department of Public Health, Henri-Mondor Hospital (AP-HP), University Paris XII, Créteil, France*

Correspondence: Dr J Revuz, Service de Dermatologie, Hôpital Henri Mondor – AP-HP, F-94010 Créteil Cedex, France. E-mail: jean.revuz@hmn.ap-hop-paris.fr

Abbreviations: SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis

Received 17 February 2005; revised 26 September 2005; accepted 3 October 2005; published online 22 December 2005

Table 1. Seven independent prognosis factors of Stevens–Johnson syndrome and toxic epidermal necrolysis are included in the SCORTEN

Independent prognosis factors		Weight
Age	⩾40 years	1
Malignancy	Yes	1
Body surface area detached	⩾10%	1
Tachycardia	⩾120/min	1
Serum urea	>10 mmol/l	1
Serum glucose	>14 mmol/l	1
Serum bicarbonate	<20 mmol/l	1
SCORTEN		7

Malignancy: evolving cancer and haematological malignancies.
SCORTEN represents the number of abnormal variables among the seven independent prognosis factors (a weight of 1 was assigned to each independent variable).

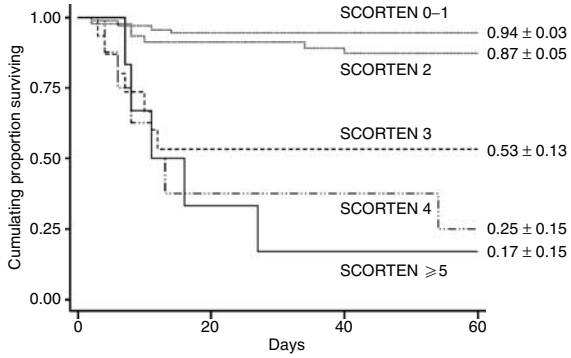

Figure 1. Survival curves according to the SCORTEN at day 1. The probability of hospital mortality over time was determined using Kaplan–Meier survival analysis.

survival ranged from 0.94 (0.03) for a score below 2 to 0.17 (0.15) for a score of 5 or higher.

Evolution of SCORTEN over time

For the majority (90) of the 144 patients included in this study, the computed SCORTEN did vary during the first 5 days of hospitalization. Friedman's test evidenced an overall significant difference between scores ($P=0.001$), which was related to a significant increase between days 1 and 4 ($P=0.05$, Dunn's multiple comparisons test) (Table 2). This increase was not related to the progression of any specific item (data not shown). In multivariate analyses, on whichever day collected, from day 1 to day 5 of hospitalization, all seven SCORTEN variables were independently associated with a greater risk of death (data not shown). The SCORTEN itself was associated with a greater risk of death on each of the first 5 days of hospitalization.

Assessment of successive SCORTEN performance

Calibration and discrimination of the successive SCORTEN were excellent. The high *P*-value of the Hosmer–Lemeshow statistic indicated an excellent agreement (calibration) between the observed and expected numbers of deaths (all *P*-values >0.30; Table 3). The overall agreement between the expected and observed numbers of deceased patients was the highest on day 3. On days 1 and 2, SCORTEN tended to underestimate the mortality for patients with a low SCORTEN (0–1), while on day 5 it tended to overestimate the mortality rate for patients with a SCORTEN of 1 or 2. The discriminatory power of the score was excellent: all the areas under receiver operating characteristic (ROC) curve were above 80% (Table 3).

Highest SCORTEN value

The highest SCORTEN value obtained during the first 5 days of hospitalization was dramatically associated to the mortality. The hospital mortality was 0% (95% confidence interval 0–8.2) when the highest SCORTEN was 0 or 1; 6.7% (1.4–18.3) when it reached 2; 23.8% (8.2–47.2) when it reached 3; 35.3% (14.2–61.7) when it reached 4; and 77.8% (52.4–93.6) when it reached or exceeded 5.

Influence of admission delay on the clinical evolution

The admission delay did not differ between deceased patients and survivors: 80% of the survivors and 86% of the deceased had an admission delay lower than or equal to 7 days, with a mean admission delay of 5.2 days (±3.2) among survivors *versus* 5.7 days (±5.0) among deceased patients ($P=0.8$). The SCORTEN adjusted for the delay was similar to the crude SCORTEN, whether the delay was considered as a quantitative value or dichotomized according to the median value, or quartiles. In all cases, the SCORTEN adjusted on the delay retained the same predictive value as the SCORTEN itself.

DISCUSSION

This study established an additional validation of the SCORTEN. On each of the first 5 days of hospitalization, the formally tested calibration demonstrated an excellent agreement between expected and observed numbers of deaths. The discriminatory power was also excellent, with receiver operating characteristic areas all above 80%. This study showed that, although SCORTEN varies during the first 5 days of hospitalization, the score's validity is not altered. SCORTEN retains its predictive power on whichever day of hospitalization it is calculated, even in the case of late deaths (after more than 15 days of hospitalization). Another purpose of this study was to determine the influence of admission delay. This study brought to light the fact that the admission delay does not affect significantly prognosis nor SCORTEN's value.

SJS and TEN are acute, potentially life-threatening conditions. The overall mortality rate observed in our series (19.4%) was consistent with those previously reported. The low incidence rates of TEN and SJS (around 1.5 and 2 cases per million population per year) do not allow the collection of very large databases. To obtain sufficient numbers and

Table 2. Relative risk of death associated with the SCORTEN on the first 5 days of hospitalization

	Day 1	Day 2	Day 3	Day 4	Day 5
Total number of patients	**144**	**144**	**142**	**141**	**139**
SCORTEN, mean±1 SD[1]	1.74±1.22	1.90±1.41	1.92±1.41	1.99±1.43	1.88±1.45
Maximal value	5	6	6	6	6
SCORTEN (Nb (%))[2]					
0–1	69 (47.9)	64 (44.4)	62 (43.7)	57 (40.4)	66 (47.5)
2	46 (31.9)	43 (29.9)	41 (28.9)	42 (29.8)	32 (23.0)
3	15 (10.4)	14 (9.7)	19 (13.4)	21 (14.9)	23 (16.5)
4	8 (5.6)	15 (10.4)	12 (8.5)	12 (8.5)	9 (6.5)
⩾5	6 (4.2)	8 (5.6)	8 (5.6)	9 (6.4)	9 (6.5)
SCORTEN, OR (95% CI)[3]	3.43 (2.15–5.48)	3.01 (2.01–4.51)	3.67 (2.27–5.94)	3.43 (2.15–5.46)	3.94 (2.32–6.67)

[1]SCORTEN represents the number of abnormal variables among the seven independent prognosis factors (a weight of 1 was assigned to each independent variable): (1) overall difference between scores: $P<0.001$ (Friedman's test); (2) score increase between days 1 and 4: $P=0.05$ (Dunn's test).
[2]Number of patients (percentage).
[3]OR, odds ratio corresponds to one score point. SD, standard deviation; CI, confidence interval.

Table 3. Performance of the SCORTEN on each of the first 5 days of hospitalization

	Day 1	Day 2	Day 3	Day 4	Day 5
Total number of patients	**144**	**144**	**142**	**141**	**139**
No. of deaths: expected/ observed at discharge	E/O	E/O	E/O	E/O	E/O
SCORTEN					
0–1	2.2/4	1.9/4	1.9/1	1.7/0	2.0/1
2	5.6/6	5.2/3	5.0/5	5.1/6	3.9/2
3	4.9/7	4.5/5	6.2/6	6.8/5	7.4/7
4	5.0/6	9.3/9	7.5/7	7.5/7	5.6/6
⩾5	5.1/5	7.0/7	7.1/7	8.0/7	8.0/7
Total	22.7/28	28.0/28	27.6/26	29.0/25	26.9/23
P-value (calibration)[1]	>0.30	>0.30	>0.90	>0.30	>0.50
AUC (95% CI)[2]	83% (76–89%)	83% (76–89%)	88% (82–93%)	88% (81–93%)	90% (84–94%)

[1]*P*- value of the Hosmer–Lemeshow statistic, indicating the agreement between the expected and observed numbers of death; a high *P*-value indicates a good agreement.The expected mortality rate (number of deceased patients) predicted by the SCORTEN is calculated using the formula: $P(\text{death})=e^{\text{logit}}/1+e^{\text{logit}}$ where logit=−4.448+1.237(SCORTEN).
[2]AUC (95% confidence interval): areas under receiver operating characteristic curves with 95% exact binomial confidence intervals.

proceed with the analysis, we included 144 patients over a long time period: from January 1993 to October 2003. Thus, two-thirds of the patients had been included in our previous study (1993–1998). The therapeutic management of patients did not change during this period, nor did the mortality rates.

We looked at the first 5 days of hospitalization, to check if an early reassessment of the SCORTEN would improve the disease outcome prediction. It was the shortest length of stay in patients with ''benign'' disease, and most patients reached the peak of their disease during the first 5 days of their hospitalization. Similarly, in acute pancreatitis, several severity-of-illness scores have been developed with a day 1 and day 3 score assessment (Larvin and McMahon, 1989).

The score performance was excellent from days 1 to 5, and SCORTEN's discriminatory power seemed to improve over time. The overall agreement between the expected and observed numbers of deceased patients was the highest on days 2 and 3 of hospitalization. On the other hand, the

agreement inside each SCORTEN category was the most discriminating on day 3 of hospitalization: the SCORTEN predicted most accurately the mortality rate when calculated on that day. In cases of patients with a low SCORTEN (0–1), on days 1 and 2, the expected number of deaths was slightly lower than what was observed; on days 4 and 5, it was slightly higher. In cases of patients with a high SCORTEN (3–7), there was a high correlation between the expected and observed numbers of death from days 1–5. The highest SCORTEN computed from days 1–5 predicted the probability of death even more accurately than the day 1 SCORTEN.

The fact that admission delay did not affect prognosis significantly could be explained by an earlier admission of the severest cases: among the patients, there may be rapid and slow progressors with different mortality rates, a hypothesis that would deserve further investigation.

The development of a reliable score allowing to predict disease outcome in TEN patients has proven useful. The probability of hospital mortality is an objective assessment that can help clinicians when discussing patients' prognosis with family members or medical staff. It has been argued that the SCORTEN, developed in France, may not be applicable to populations in other countries. A recent American study retrospectively analyzed 24 patients with TEN and showed that the SCORTEN can accurately predict mortality in patients receiving supportive intensive care outside Europe (Trent *et al.*, 2004).

In addition, evaluation of new treaments is more reliable if investigators are able to rate the patients' severity-of-illness. SCORTEN has thus been used by several teams in various trials, trying to assess the efficacy of intravenous immunoglobulin for the treatment of TEN (Bachot *et al.*, 2003; Campione *et al.*, 2003; Trent *et al.*, 2003; Brown *et al.*, 2004).

Our study demonstrates that, although SCORTEN varies during hospitalization, its performance is excellent, with a predictive value at its best on day 3. We therefore recommend to recompute SCORTEN on day 3 of hospitalization. Both day 1 and 3 SCORTEN's evaluations are helpful nowadays to sharpen prognostic estimation when merely symptomatic measures can be proposed in epidermal necrolysis management. Nevertheless, assessing patients' prognosis is most relevant at the very beginning of a disease's course, especially when a specific therapy is instituted. When this be the case for epidermal necrolysis, the day 1 SCORTEN will then be the most useful for evaluating the potential benefit of that treatment.

MATERIALS AND METHODS

Patients

Medical charts of all consecutive patients admitted to the dermatology intensive care unit at Henri Mondor hospital from January 1993 to October 2003 were retrospectively reviewed. Patients were eligible if the discharge diagnosis was SJS ($n=55$; deceased = 5.5%), SJS/TEN overlap ($n=50$; deceased = 18%), or TEN ($n=39$; deceased = 41%) (Bastuji-Garin *et al.*, 1993). The diagnosis was confirmed by skin biopsy showing full thickness necrosis of the epidermis and a negative direct immunofluorescence test. In all, 51 patients who participated in therapeutic trials of thalidomide ($n=15$) (Wolkenstein *et al.*, 1998) or intravenous immunoglobulin ($n=36$) (Bachot *et al.*, 2003) were not included. Therefore, the present study included only patients who were managed according to our usual procedures (Roujeau and Stern, 1994) and did not receive any ''specific'' treatment such as corticosteroids, intravenous immunoglobulin, or immunosuppressive therapy. The medical ethical committee of the University of Paris XII approved all described studies.

Clinical and biological data

The seven SCORTEN variables (Table 1) collected from day 1 (admission day) to day 5 were extracted from medical charts (Bastuji-Garin *et al.*, 2000). The SCORTEN was then calculated on each of the first 5 days of hospitalization for each patient.

Admission delay was defined as the delay between the onset of the disease (probable index day) and the admission day. The probable index day was determined by the first involvement of skin or mucous membranes not explained by other conditions and followed within 3 days by a definite sign (erosions or blisters), as defined previously (Roujeau *et al.*, 1995).

Analyses

The end point was the outcome at hospital discharge. The probability of hospital mortality over time was analyzed (Kaplan and Meier, 1958). Survival curves according to the day 1 SCORTEN were compared by using the log-rank test.

The successive SCORTEN were compared by using a nonparametric analysis of variance for repeated measures (Friedman's test); in case of significant variations, Dunn's multiple comparisons test was performed.

SCORTEN variables, as well as the SCORTEN itself, were compared between patients who died during hospitalization and survivors by logistic regression models. Odds ratios were estimated with their 95% confidence intervals (95% confidence interval).

The performance of the successive SCORTEN was assessed from day 1 to 5. The expected mortality rate predicted by the SCORTEN was calculated using the formula: $P\,(\text{death}) = e^{\text{logit}}/1 + e^{\text{logit}}$ where $\text{logit} = -4.448 + 1.237(\text{SCORTEN})$ (Bastuji-Garin *et al.*, 2000). Calibration, that is, correspondence between the estimated probabilities of mortality produced by the model and the actual mortality, was evaluated (Lemeshow and Hosmer, 1982). The discriminatory power was evaluated by using nonparametric receiver operating characteristic analyses (Hanley and McNeil, 1982).

We also evaluated the mortality rates (and 95% confidence interval) according to the highest SCORTEN value during the first 5 days of hospitalization.

In order to analyze the potential influence of admission delay on mortality, we compared admission delays between deceased patients and survivors; the day 1 SCORTEN was then adjusted for this delay in a logistic regression model.

Quantitative variables were reported as mean ± 1 standard deviation, except when otherwise indicated; categorical variables were reported as number (percentages).

Data were analyzed using the Stata Statistical software (StataCorp 2003, Release 8.0, College Station, TX).

CONFLICT OF INTEREST

The authors state no conflict of interest.

REFERENCES

Bachot N, Revuz J, Roujeau JC (2003) Intravenous immunoglobulin treatment for Stevens–Johnson syndrome and toxic epidermal necrolysis. *Arch Dermatol* 139:33–6

Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P (2000) SCORTEN: a Severity of Illness Score for Toxic Epidermal Necrolysis. *J Invest Dermatol* 115:149–53

Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC (1993) Clinical classification of cases of toxic epidermal necrolysis, Stevens–Johnson syndrome, and erythema multiforme. *Arch Dermatol* 129:92–6

Brown KM, Silver GM, Halerz M, Walaszek P, Sandroni A, Gamelli RL (2004) Toxic epidermal necrolysis: does immunoglobulin make a difference? *J Burn Care Rehabil* 25:81–8

Campione E, Marulli GC, Carrozzo AM, Chimenti MS, Costanzo A, Bianchi L (2003) High-dose intravenous immunoglobulin for severe drug reactions: efficacy in toxic epidermal necrolysis. *Acta Dermatol Venereol* 83:430–2

Hanley JA, McNeil BJ (1982) The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 143:29–36

Kaplan EL, Meier P (1958) Non parametric estimation from incomplete observations. *J Am Stat Assoc* 53:457–81

Larvin M, McMahon MJ (1989) APACHE-II score for assessment and monitoring of acute pancreatitis. *Lancet* 2:201–5

Lemeshow S, Hosmer DW (1982) A review of goodness of fit statistics for use in the development of logistic regression models. *Am J Epidemiol* 115:92–106

Roujeau JC, Kelly JP, Naldi L, Rzany B, Stern RS, Anderson T *et al.* (1995) Medication use and the risk of Stevens–Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med* 333:1600–7

Roujeau JC, Stern RS (1994) Severe adverse cutaneous reactions to drugs. *N Engl J Med* 331:1272–85

Trent JT, Kirsner RS, Romanelli P, Kerdel FA (2003) Analysis of intravenous immunoglobulin for the treatment of toxic epidermal necrolysis using SCORTEN: the Univeristy of Miami Experience. *Arch Dermatol* 139:39–43

Trent JT, Kirsner RS, Romanelli P, Kerdel FA (2004) Use of SCORTEN to accurately predict mortality in patients with toxic epidermal necrolysis in the United States. *Arch Dermatol* 140:890–2

Wolkenstein P, Latarjet J, Roujeau JC, Duguet C, Boudeau S, Vaillant L *et al.* (1998) Randomised comparison of thalidomide *versus* placebo in toxic epidermal necrolysis. *Lancet* 352:1586–9